Some Alkyl and Acyl Derivatives of 2-Phenacylpyridine.

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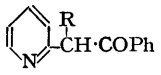
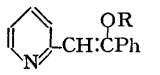
Alkylation of 2-phenacylpyridine with methyl, ethyl, propyl, and allyl halides gives *C*-alkyl derivatives exclusively, whereas 2-dimethylaminoethyl chloride causes *O*-alkylation. Acetylation gives the *O*-derivative but aroylation gives *C*-derivatives. Chemical and ultra-violet absorption data are presented in support of the structures assigned.

2-Phenacylpyridine, in the enolic form (II; R = H), reacts with cupric ions to form a cupric chelate compound (Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301). Substitution of the methylene group of 2-phenacylpyridine has now been investigated in an attempt to vary the keto–enol ratio and the complexing properties of the system.

The sodio-derivative of 2-phenacylpyridine, prepared from 2-phenacylpyridine and powdered sodamide in toluene or by sodium methoxide in methanol, can react with acid anhydrides and alkyl and acyl halides to give the *C*- (I) or and the *O*-derivatives (II). Methyl iodide and benzyl chloride in toluene gave exclusively the *C*-alkyl compounds.

(I)   (II)

Solvents possessing higher dielectric constants than toluene were necessary for alkylations involving allyl, ethyl, and *n*-propyl bromide, and these halides also yielded *C*-derivatives (60—70% yield). Spectroscopic data indicated the absence of *O*-alkyl compounds even in the crude products from the above reactions. 2-Dimethylaminoethyl chloride in a solvent of equal parts of toluene and acetone gave the enol ether (78% yield) (II; R = $CH_2{\cdot}CH_2{\cdot}NMe_2$). From a consideration of hydrolysis experiments and ultra-violet absorption measurements, it was reported (Sperber, Fricano, and Papa, *ibid.*, 1950, **72**, 3068) that *C*-alkylation also occurred in this reaction, but we could not detect the presence of any amino-ketone. The alkylation of diphenylacetone with this halide also gave *O*-alkylation exclusively (Rinderknecht, *ibid.*, 1951, **73**, 5770) under conditions which yielded principally *C*-derivatives with non-basic alkyl halides. 2-Dimethylaminoethyl chloride is known (Knorr, *Ber.*, 1904, **37**, 3507; Simonella, Madrone, and Favini, *Gazzetta*, 1950, **80**, 129) to form cyclic 'onium cations in polar solvents; however, we obtained the *C*-benzyl compound of 2-phenacylpyridine when using benzyldimethylanilinium chloride.

The sodio-derivative of 2-phenacylpyridine in toluene with *p*-nitro- and *p*-chlorobenzoyl chloride gave the *C*-aroyl derivatives (70% yield), as did benzoic anhydride and 3 : 5-dinitrobenzoyl chloride in toluene–acetone, whereas acetic anhydride reacted readily with the sodio-derivative in toluene to give the *O*-derivative (75% yield). Attempted acylation of 2-phenacylpyridine by propionic and butyric anhydrides failed, as did attempted benzoylation, with benzoic anhydride, of 1-2′-pyridylbutan-2-one and 1-2′-pyridylpentan-2-one. The known ease of hydrolysis of 1 : 3-diarylpropane-1 : 3-diones by dilute alkalis (Bradley and Robinson, *J.*, 1926, 2356) may account for the recovery of starting material from these unsuccessful acylations.

Table 1. *Ultra-violet spectra, in ethanol, of 2-phenacylpyridine and its C-alkyl derivatives.*

R =	H	Me	Et	Pr^n	$CH_2{\cdot}CH{:}CH_2$	CH_2Ph
$\lambda_{max.}$ (mμ)	244	247	247	247	247	247
$\varepsilon_{max.}$	10,700	13,800	14,000	12,300	13,000	15,400

Sperber *et al.* (*loc. cit.*) found that the ultra-violet absorption, in ethanol, of deoxybenzoin ($\lambda_{max.}$ 243 mμ), α-ethyldeoxybenzoin ($\lambda_{max.}$ 245 mμ), and 2-phenacylpyridine ($\lambda_{max.}$ 246 mμ) are similar. Table 1 indicates that the compounds listed are *C*-alkyl derivatives of 2-phenacylpyridine. The styryl derivatives of pyridine and benzene exhibit a high-intensity

absorption band in the region 295—310 mμ (Blout and Eager, *J. Amer. Chem. Soc.*, 1945, **67**, 1315). The structures of the *O*-derivatives of 2-phenacylpyridine (II; R = $-CH_2 \cdot CH_2 \cdot NMe_2$ or Ac) are indicated by the fact that their ultra-violet spectra resemble those of 2-stilbazole and stilbene (see Table 2).

TABLE 2. *Absorption spectra in ethanol.*

	2-Stilbazole *	Silbene *	(II; R = $CH_2 \cdot CH_2 \cdot NMe_2$)	(II; R = Ac)
$\lambda_{infl.}$ (mμ)	275—285	—	270—280	275—285
$\lambda_{max.}$	310	295	302—304	300—302
$\varepsilon_{max.}$	27,600	26,300	22,200	24,100

* Blout and Eager, *loc. cit.*

The ease of regeneration of 2-phenacylpyridine from its 2-dimethylaminoethyl derivative with 2N-sulphuric acid contrasts with the failure of the alkyl derivatives of Table 1 to hydrolyse under similar conditions and substantiates the structures assigned.

Evidence that aroylation gave *C*-derivatives was obtained by the preparation of 1-*p*-chlorophenyl-3-phenyl-2-2′-pyridylpropane-1 : 3-dione (I; R = $CO \cdot C_6H_4Cl$-*p*) by two independent methods. Aroylation of 2-phenacylpyridine with *p*-chlorobenzoyl chloride and of 2-*p*-chlorophenacylpyridine with benzoic anhydride yielded compounds which were identical in m. p. and spectroscopic data. Table 3 shows that the ultra-violet spectra of

TABLE 3. *Absorption spectra in ethanol* (λ *in* mμ) *of* C-*aroyl derivatives of* 2-*phenacylpyridine.*

(II; R = Bz)	$\lambda_{max.}$	251	310	370	$\lambda_{min.}$	—	280	332
	$\varepsilon_{max.}$	17,500	7,800	9,000	$\varepsilon_{min.}$	—	6,600	6900
(II; R = $CO \cdot C_6H_4Cl$-*p*)	$\lambda_{max.}$	255	310	370	$\lambda_{min.}$	230	283	326
	$\varepsilon_{max.}$	17,200	8,900	11,500	$\varepsilon_{min.}$	12,700	8,300	8500
(II; R = $CO \cdot C_6H_4 \cdot NO_2$-*p*)	$\lambda_{max.}$	255 *	—	370	$\lambda_{min.}$	—	—	325
	$\varepsilon_{max.}$	19,200	—	13,900	$\varepsilon_{min.}$	—	—	9000
[II; R = $CO \cdot C_6H_3 \cdot (NO_2)_2$-1 : 3 : 5]...	$\lambda_{max.}$	—	292	370	$\lambda_{min.}$	—	280	320
	$\varepsilon_{max.}$	—	10,000	12,600	$\varepsilon_{min.}$	—	10,200	7700

* Infl. 285 mμ (ε 15,000).

the other aroyl derivatives resemble that of the *p*-chlorophenacylpyridine derivative. These derivatives, in contrast to the other compounds reported, gave green colours in alcoholic ferric chloride. The picrate of 2-phenacylpyridine was obtained on attempting to prepare the picrates of these *C*-aroyl derivatives, in contrast to the reaction of *C*-alkyl and *O*-derivatives, which yield normal picrates.

The metal chelating properties of these compounds are being investigated in relation to their bacteriostatic activity.

EXPERIMENTAL

Ultra-violet absorption spectra were determined in absolute ethanol, with a Unicam S.P. 500 spectrophotometer, cell-path 1 cm. Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equiv. wts., except those of picrates, were determined by titration with 0·02N-perchloric acid in acetic acid; those of the picrates were determined by titration with 0·02N-sodium hydroxide in 1 : 1 ethanol–acetone with ethyl bis-2 : 4-dinitrophenylacetate as indicator.

Alkylation.—2-Phenacylpyridine with alkyl halides. The sodio-derivative of 2-phenacylpyridine, prepared by heating 2-phenacylpyridine (0·7 g., 0·004 mole) and sodamide (0·22 g.) in toluene (20 ml.) for 3 hr. at 80°, was heated with the alkyl halide (0·005 mole) at the temperature, and for the time, and in the solvent stated. The mixture was then cooled, aqueous ammonium chloride added, the organic layer separated, and the aqueous layer extracted with ether. The organic extracts were combined, washed with water, and dried ($MgSO_4$), and the solvent removed under reduced pressure to yield products which were purified by chromatography on alumina.

Products were recrystallised from ethanol unless otherwise stated.

Methyl iodide (40°; 3 hr.; toluene) gave α-2′-*pyridylpropiophenone* (I; R = Me) (64%), white rosettes, m. p. 64·5° (Found: C, 79·8; H, 6·2; N, 6·7%; equiv., 214. $C_{14}H_{13}ON$ requires C, 79·55; H, 6·15; N, 6·6%; equiv., 211).

Benzyl chloride (80°; 2 hr.; toluene) gave β-*phenyl*-α-2′-*pyridylpropiophenone* (I; R = CH_2Ph) (70%), white rosettes, m. p. 97—98° (Found: C, 83·8; H, 5·8; N, 4·8%; equiv., 289. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9; N, 4·9%; equiv., 287).

Benzyldimethylanilinium chloride (50°; 4 hr.; acetone–toluene) gave β-phenyl-α-2′-pyridylpropiophenone (66%), m. p. and mixed m. p. 97—98°.

Propyl bromide (50°; 12 hr.; acetone–toluene) gave α-2′-*pyridylvalerophenone* (I; R = Pr^n) (72%), a colourless oil, n_D^{20} 1·5640 (Found: C, 80·5; H, 7·5%; equiv., 244. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2%; equiv., 239). It gave a *picrate*, yellow prisms, m. p. 146—147° (Found: C, 56·8; H, 4·4; N, 12·3%; equiv., 470. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·35; N, 12·0%; equiv., 468).

Allyl bromide (50°; 12 hr.; acetone–toluene) gave α-2′-*pyridylpent*-4-*enophenone* (I; R = CH_2·CH·CH_2) (75%), a colourless oil, n_D^{20} 1·5772 (Found: C, 81·6; H, 6·5%; equiv., 241. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4%; equiv., 237). It gave a *picrate*, orange prisms, m. p. 130—131° (Found: C, 56·4; H, 4·0; N, 11·8%; equiv., 467. $C_{22}H_{18}O_8N_4$ requires C, 56·6; H, 3·9; N, 12·0%; equiv., 466).

2-Dimethylaminoethyl chloride (50°; 12 hr.; acetone–toluene) gave α-2′-*dimethylaminoethoxy*-β-2′-*pyridylstyrene* (II; R = CH_2·CH_2·NMe_2) (78%), a colourless oil, n_D^{20} 1·5855 (Found: C, 75·4; H, 7·8; N, 10·0%; equiv., 137. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5; N, 10·4%; equiv., 134). Hydrolysis of the enol ether with 2N-sulphuric acid gave 2-phenacylpyridine. A *dipicrate* was prepared from the oil, and formed yellow prisms, m. p. 135° (decomp.) (Found: C, 48·5; H, 3·8; N, 15·2; equiv., 718. $C_{29}H_{26}O_{15}N_8$ requires C, 49·0; H, 3·9; N, 15·0%; equiv., 726).

Ethyl iodide (0·005 mole) and a solution of the sodio-derivative of 2-phenacylpyridine from 2-phenacylpyridine (0·75 g., 0·004 mole) and sodium (0·13 g.) in methanol (20 ml.) were heated at 50° for 0·5 hr. The methanol was distilled off and the mixture treated, as described in the general method, to yield α-2′-*pyridylbutyrophenone* (I; R = Et) (63%), white rosettes, m. p. 50° (Found: C, 79·6; H, 6·5; N, 6·5%; equiv., 227. $C_{15}H_{15}ON$ requires C, 79·9; H, 6·6; N, 6·2%; equiv., 225). Sperber *et al.* (*loc. cit.*) reported this compound as an oil, n_D^{25} 1·5830.

Acylation.—2-Phenacylpyridine with acid anhydrides and acyl halides. The sodio-derivative of 2-phenacylpyridine (0·005 mole) was treated with the acid anhydride or aroyl halide (0·006 mole) as described under "Alkylation." The products were crystallised from ethanol.

Acetic anhydride (50°; 0·5 hr.; toluene) gave α-*acetoxy*-β-2′-*pyridylstyrene* (II; R = Ac) (74%), yellow prisms, m. p. 94° (Found: C, 75·0; H, 5·4; N, 5·8%; equiv., 242. $C_{15}H_{13}O_2N$ requires C, 74·9; H, 5·4; N, 5·95%; equiv., 239). Hydrolysis of the enol ester with 2N-sulphuric acid gave 2-phenacylpyridine. It gave a *picrate*, yellow prisms, m. p. 159° (Found: C, 53·8; H, 3·5; N, 12·1%; equiv., 468. $C_{21}H_{16}O_9N_4$ requires C, 53·4; H, 3·4; N, 12·0%; equiv., 468).

Benzoic anhydride (50°; 2 hr.; acetone–toluene) gave 1 : 3-diphenyl-2-2′-pyridylpropane-1 : 3-dione (I; R = Bz) (75%), light yellow needles, 141·5° (Found: C, 79·4; H, 5·0; N, 4·9. Calc. for $C_{20}H_{15}O_2N$: C, 79·7; H, 5·0; N, 4·7%). Kloppenburg and Wibaut (*Rec. Trav. chim.*, 1946, **65**, 393) reported a compound, m. p. 140°, as a by-product (0·07% yield) from the reaction of benzoic anhydride on 2-picolyl-lithium.

p-Nitrobenzoyl chloride (50°; 2 hr.; toluene) gave 1-p-*nitrophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (I; R = CO·C_6H_4·NO_2-*p*) (75%), yellow needles, m. p. 165° (Found: C, 69·6; H, 4·1; N, 7·9. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·05; N, 8·1%).

3 : 5-Dinitrobenzoyl chloride (50°; 2 hr.; acetone–toluene) gave 1-(3 : 5-*dinitrobenzoyl*)-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (60%), yellow clusters of needles, m. p. 117—118° (Found: C, 60·7; H, 3·15; N, 10·9. $C_{20}H_{12}O_6N_3$ requires C, 61·4; H, 3·1; N, 10·7%).

1-p-*Chlorophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione.—Method* A. *p*-Chlorobenzoyl chloride (1·05 g., 0·006 mole) and the sodio-derivative of 2-phenacylpyridine (from 1 g., 0·005 mole), heated for 2 hr. at 50° in toluene, yielded 1-p-*chlorophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (75%), pale yellow prisms, m. p. 126—126·5° (Found: C, 71·3; H, 4·2; N, 4·15. $C_{20}H_{14}O_2NCl$ requires C, 71·6; H, 4·2; N, 4·2%).

Method B. 2-Chlorophenacylpyridine (1·2 g., 0·005 mole) and sodamide (0·27 g.), heated at 80° for 3 hr. in toluene (15 ml.), gave a yellow flocculent precipitate of the sodio-derivative. Benzoic anhydride (1·36 g., 0·006 mole) in acetone (15 ml.) was added to the cooled suspension at 0° and the mixture heated at 50° for 2 hr. This gave 1-*p*-chlorophenyl-3-phenyl-2-2′-pyridylpropane-1 : 3-dione (70%), pale yellow prisms, m. p. 126° (Found: C, 71·1; H, 4·15; N, 4·3%).

The compounds prepared by methods A and B were shown to be identical by mixed m. p. and ultra-violet absorption spectra.

When the above diones were heated with picric acid in ethanol they gave 2-phenacylpyridine picrate (identity checked by mixed m. p. and equiv. wt. determinations).

Other Materials.—2-Phenacylpyridine and 1-2′-pyridyl-butan-2-one, and -pentan-2-one were prepared according to Levine *et al.* (*loc. cit.*). 2-*p*-Chlorophenacylpyridine, prepared by the same method (68% yield), had m. p. 89° (cf. Smith, Stewart, Roth, and Northey, *J. Amer. Chem. Soc.*, 1948, **70**, 3997).

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